

**Additional Ablation Beyond PV
Isolation in Patients with Persistent AF**

**Keimyung University Dongsan Hospital
Hyung-Seob Park**

STAR AF II Trial

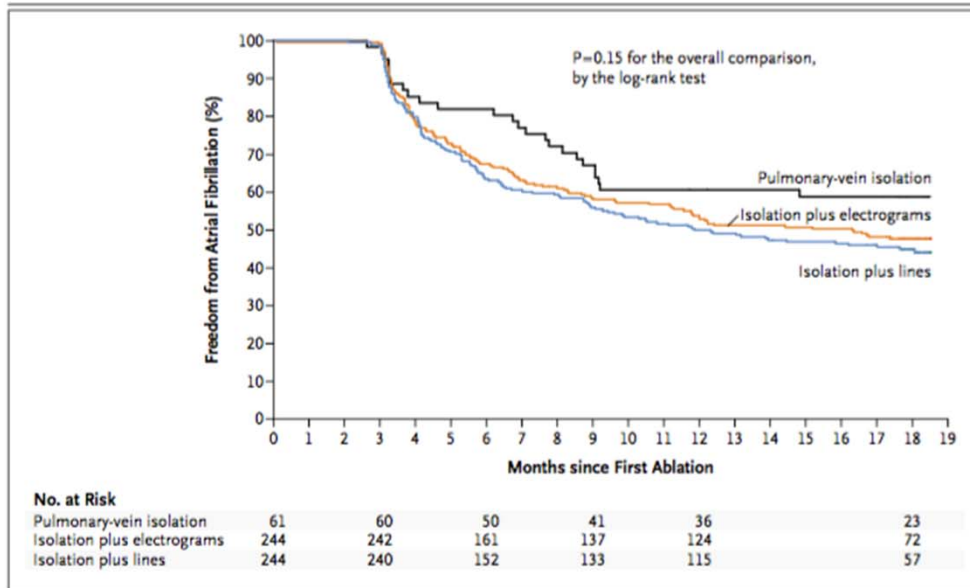
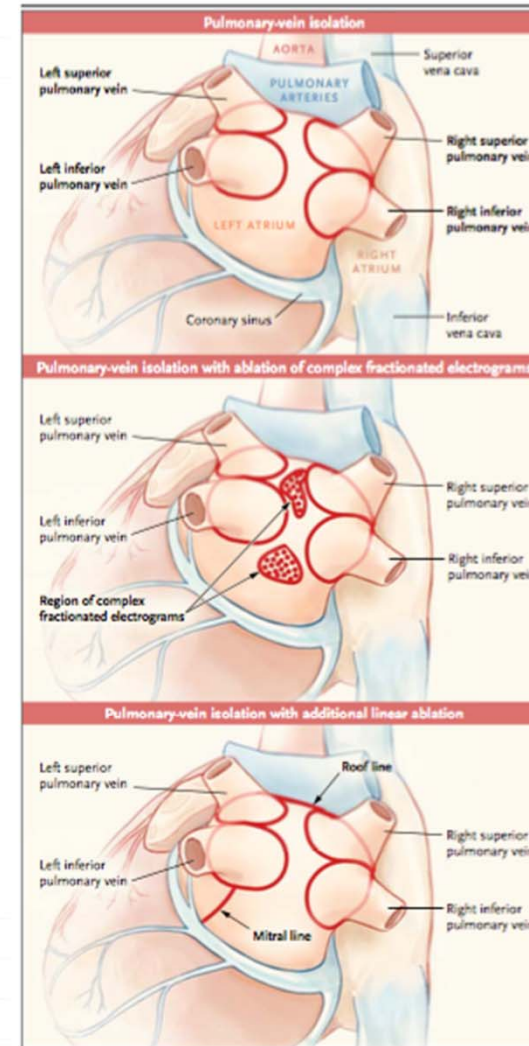


Figure 2. Freedom from Atrial Fibrillation.

The graph shows Kaplan–Meier estimates of freedom from documented atrial fibrillation more than 30 seconds after a single procedure, with or without the use of antiarrhythmic medications. There were no significant differences between groups ($P=0.15$). Isolation plus electrograms denotes ablation with pulmonary-vein isolation plus additional ablation of complex fractionated electrograms; isolation plus lines refers to ablation with pulmonary-vein isolation plus additional linear ablation.



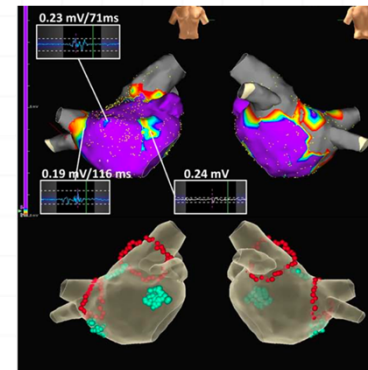
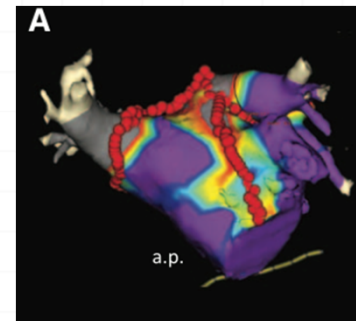
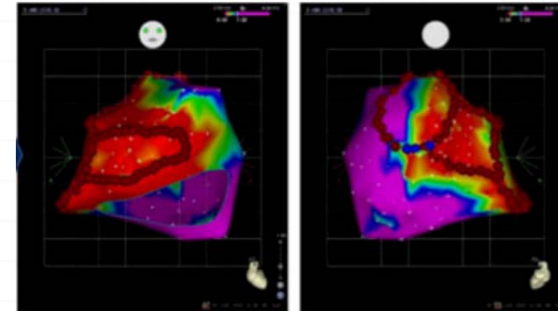
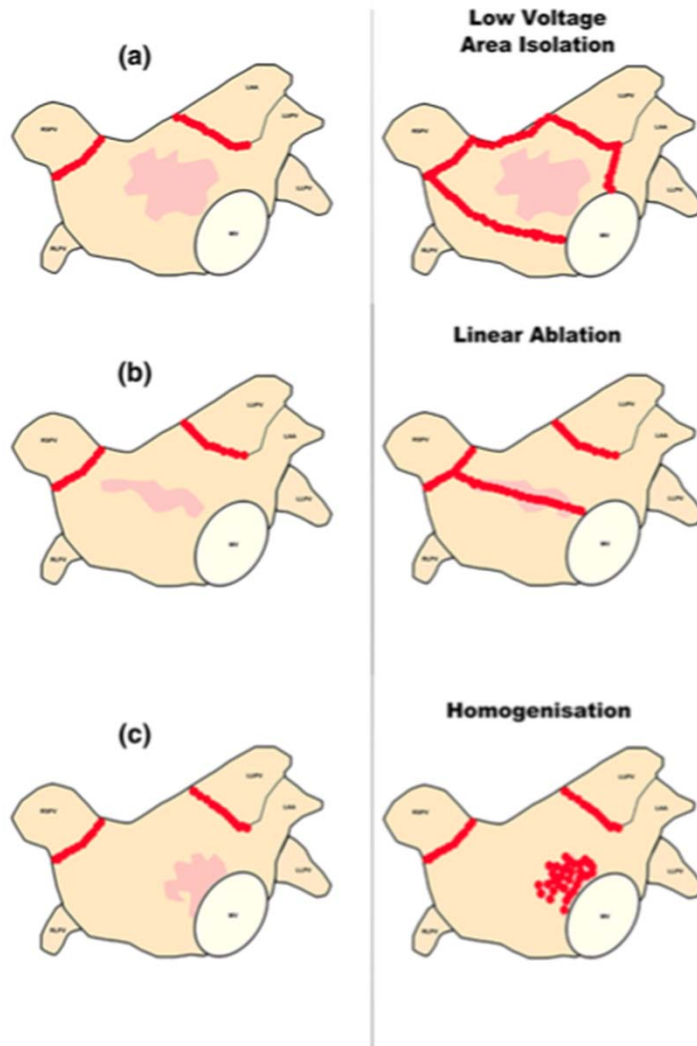
2020 ESC AF Guideline : AF Ablation Techniques

- Particularly in persistent and long-standing persistent AF, more extensive ablation has been advocated. This may include linear lesions in the atria, isolation of the LAA or of the superior vena cava, . ablation of complex fractionated electrograms, rotors, non- pulmonary foci, or ganglionated plexi, fibrosis-guided voltage and/or MRI-mapping, or ablation of high dominant frequency sites.
- However, additional benefit vs. pulmonary vein isolation (PVI) alone, justifying its use during the first procedure, is yet to be confirmed.
- A RCT-based data suggest improved outcome with targeting extrapulmonary (particularly the LAA) foci and selective ablation of low-voltage areas as adjunct to PVI.

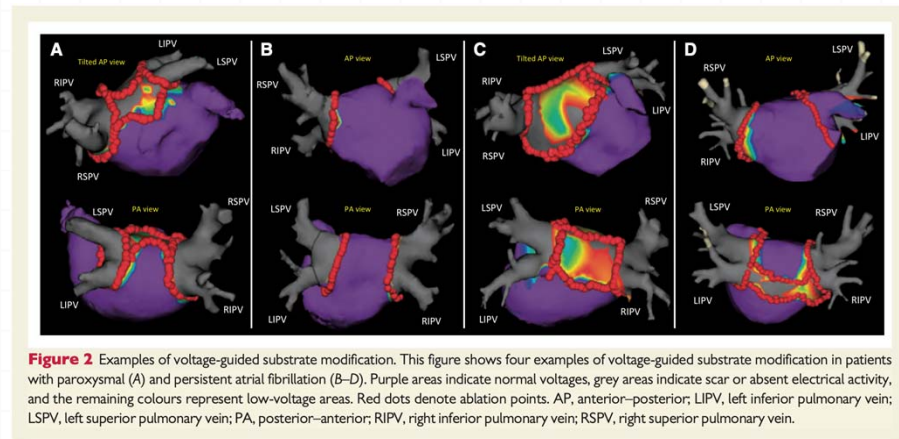
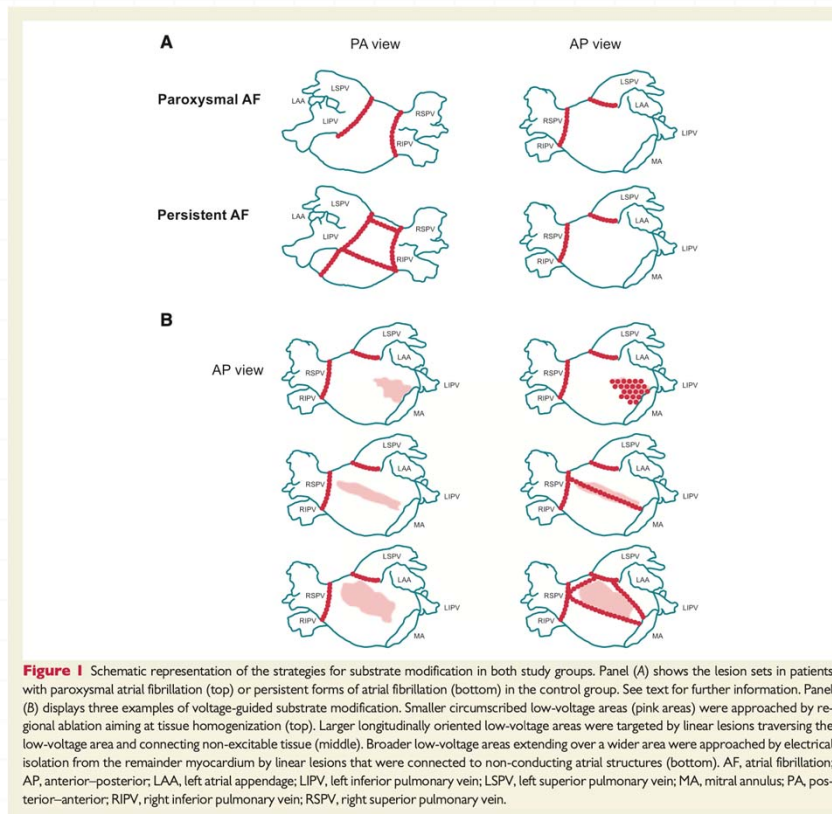
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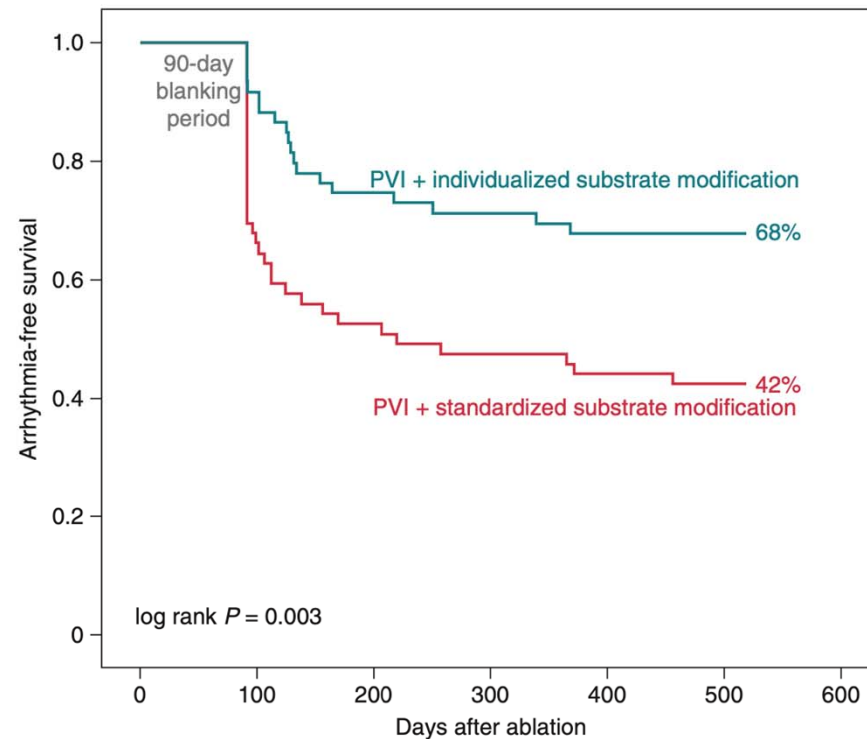
Approaches to Low Voltage Area Ablation



Voltage-guided Ablation for AF



Voltage-guided Ablation for AF



Number at risk						
Group 1	62	39	30	24	6	0
Group 2	62	54	42	39	8	2

Figure 4 Primary efficacy outcome. The Kaplan–Meier estimates of single-procedure freedom from any atrial arrhythmia >30 s off antiarrhythmic medication. PVI, pulmonary vein isolation.

Selective Voltage-Guided Ablation of AF

Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics

Amir S. Jadidi, MD; Heiko Lehrmann, MD; Cornelius Keyl, MD; Jérémie Sorrel, MD; Viktor Markstein, BSc; Jan Minners, MD; Chan-Il Park, MD; Arnaud Denis, MD; Pierre Jaïs, MD; Méléze Hocini, MD; Clemens Potocnik, MD; Juergen Allgeier, MD; Willibald Hochholzer, MD; Claudia Herrera-Siklody, MD; Steve Kim, MSEE; Youssef El Omri, MD; Franz-Josef Neumann, MD; Reinhold Weber, MD; Michel Haïssaguerre, MD; Thomas Arentz, MD

Background—Complex-fractionated atrial electrograms and atrial fibrosis are associated with maintenance of persistent atrial fibrillation (AF). We hypothesized that pulmonary vein isolation (PVI) plus ablation of selective atrial low-voltage sites may be more successful than PVI only.

Methods and Results—A total of 85 consecutive patients with persistent AF underwent high-density atrial voltage mapping, PVI, and ablation at low-voltage areas (LVA < 0.5 mV in AF) associated with electric activity lasting > 70% of AF cycle length on a single electrode (fractionated activity) or multiple electrodes around the circumferential mapping catheter (rotational activity) or discrete rapid local activity (group I). The procedural end point was AF termination. Arrhythmia freedom was compared with a control group (66 patients) undergoing PVI only (group II). PVI alone was performed in 23 of 85 (27%) patients of group I with low amount (< 10% of left atrial surface area) of atrial low voltage. Selective atrial ablation in addition to PVI was performed in 62 patients with termination of AF in 45 (73%) after 11 ± 9 minutes radiofrequency delivery. AF-termination sites colocalized within LVA in 80% and at border zones in 20%. Single-procedural arrhythmia freedom at 13 months median follow-up was achieved in 59 of 85 (69%) patients in group I, which was significantly higher than the matched control group (31/66 [47%], $P < 0.001$). There was no significant difference in the success rate of patients in group I with a low amount of low voltage undergoing PVI only and patients requiring PVI+selective low-voltage ablation ($P = 0.42$).

Conclusions—Ablation of sites with distinct activation characteristics within/at borderzones of LVA in addition to PVI is more effective than conventional PVI-only strategy for persistent AF. PVI only seems to be sufficient to treat patients with left atrial low voltage < 10%. (*Circ Arrhythm Electrophysiol.* 2016;9:e002962. DOI: 10.1161/CIRCEP.115.002962.)

Key Words: AF sources ■ atrial fibrillation ■ catheter ablation ■ fibrosis ■ low voltage ■ rotational activity



EGM + Substrate guided AF Ablation

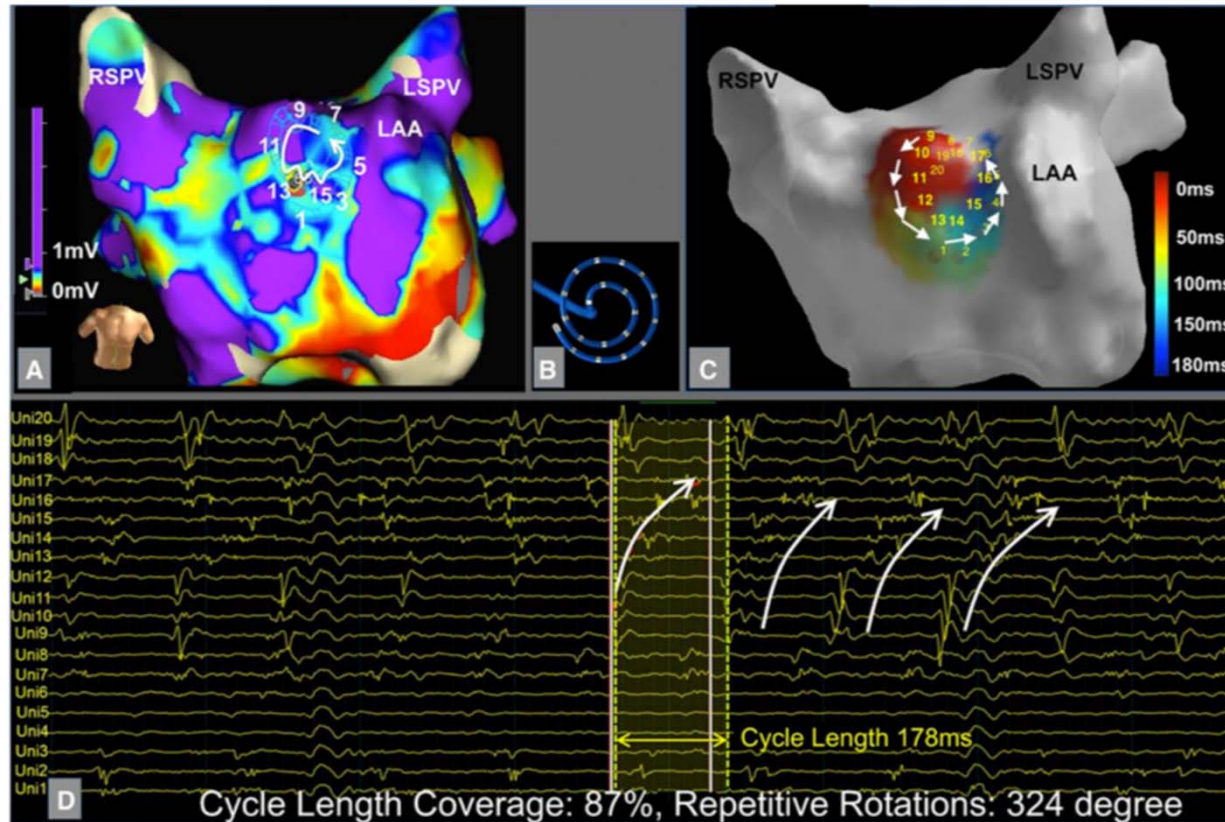


Figure 1. A–D, Voltage and regional activation sequence of electrograms on the multielectrode catheter positioned to the anteroseptum of left atrium (LA), where atrial fibrillation (AF) was terminated during later ablation. **A,** Termination of AF within low voltage <0.5 mV. Voltage mapping during ongoing AF reveals regions of low voltage <0.5 mV at LA anteroseptum. Dark marker between electrode 13 and 15 annotates the site of AF termination by radiofrequency (RF) delivery. **B,** Orientation of the circumferential mapping catheter at anteroseptal LA. **C,** Repetitive rotational activity in AF. The regional activation map illustrates the depicted AF beat of **D** displaying a repetitive sequence of rotational activity on the circumferential mapping catheter at LA anteroseptum (Movie I in the Data Supplement). **D,** Ablation of electrical activity >70% of AF cycle length terminates AF. Ablation at site of repetitive rotational activity targeting electrodes 13 to 16 with local activation gradient in unipolar recordings (coverage of >70% of AF cycle length on electrodes 7–17) terminates AF to sinus rhythm after 35 s of RF delivery. LAA indicates left atrial appendage; LSPV, left superior pulmonary vein; and RSPV, right superior pulmonary vein. (See also Figures I and II in Data Supplement for identification of rotational activity during ongoing AF.)

Selective Voltage-Guided AF Ablation

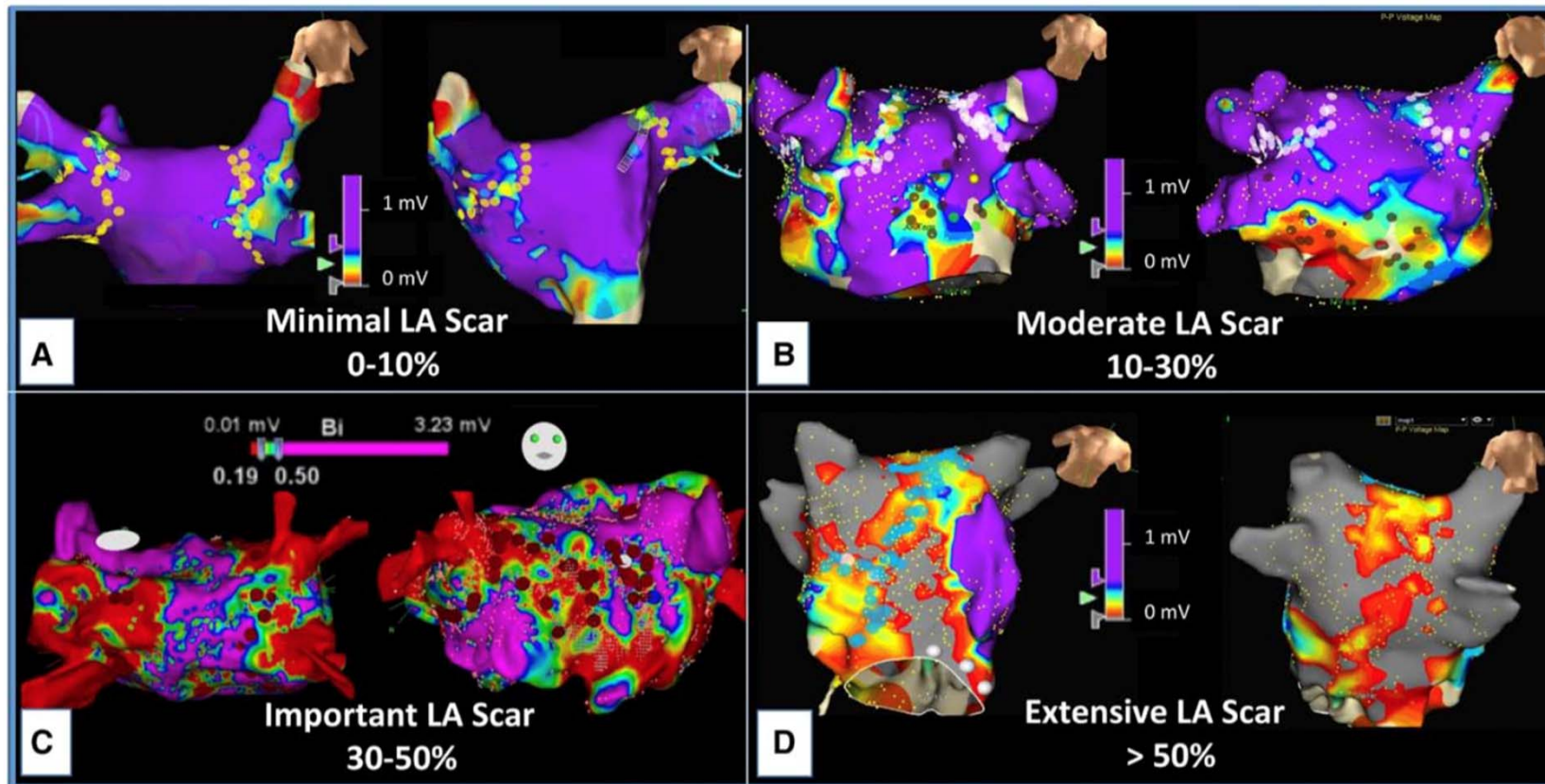
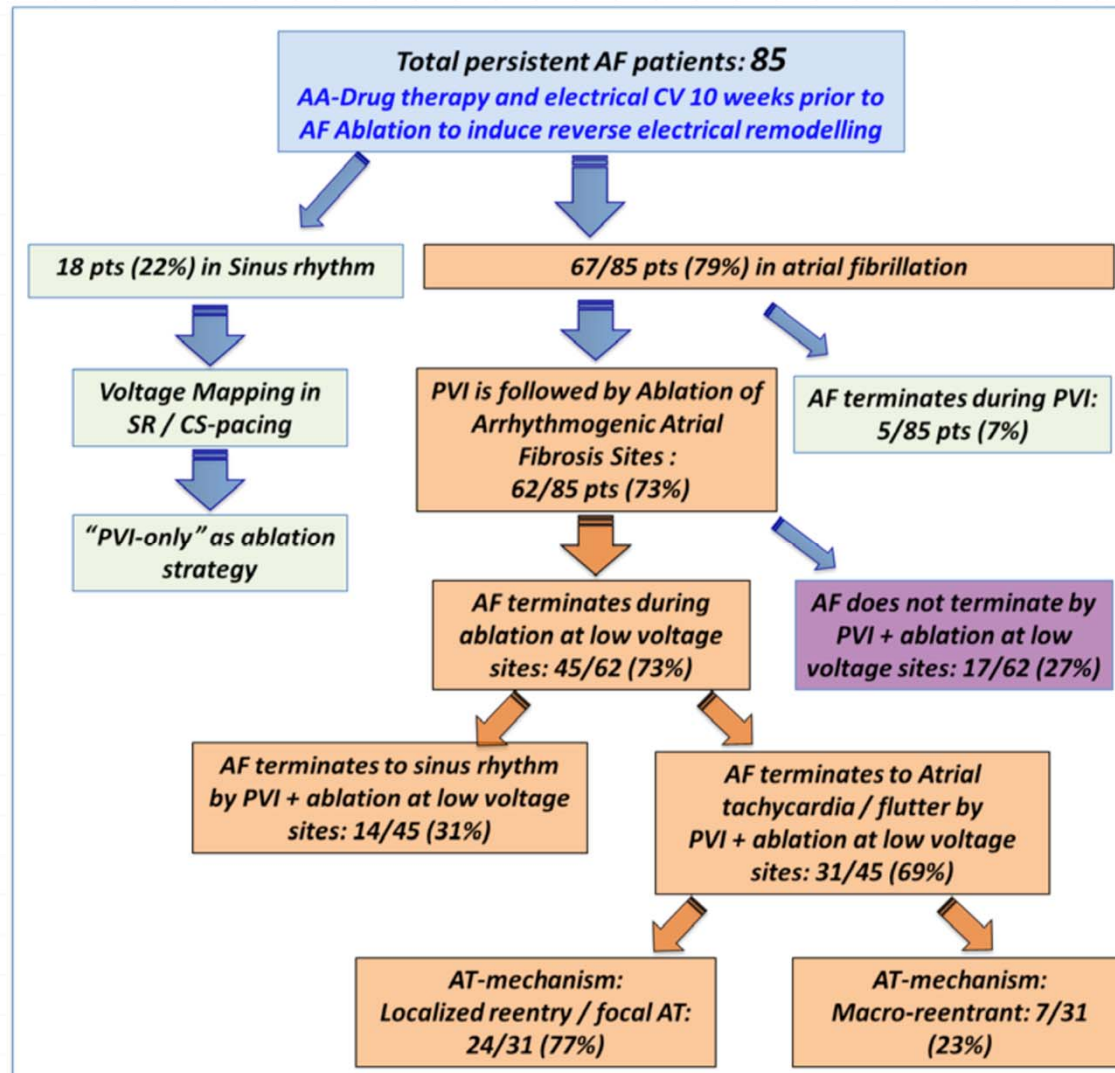


Figure 2. Low voltage-guided ablation strategy. Left atrial (LA) low-voltage pattern in patients with persistent atrial fibrillation (AF), assessed by high-density (>800 mapped sites per atrium) multielectrode mapping during ongoing AF. Low-voltage sites were defined as <0.5 mV maximum bipolar voltage. The relative extent of LA low-voltage areas was in **A**: 3%, **B**: 24%, **C**: 46%, and **D**: 76% of the total LA surface area (with exclusion of the PVs). Radiofrequency energy was applied selectively to low-voltage sites displaying electric activity >70% AF cycle length. CS indicates coronary sinus.

Selective Voltage-Guided AF Ablation



Clinical Outcome

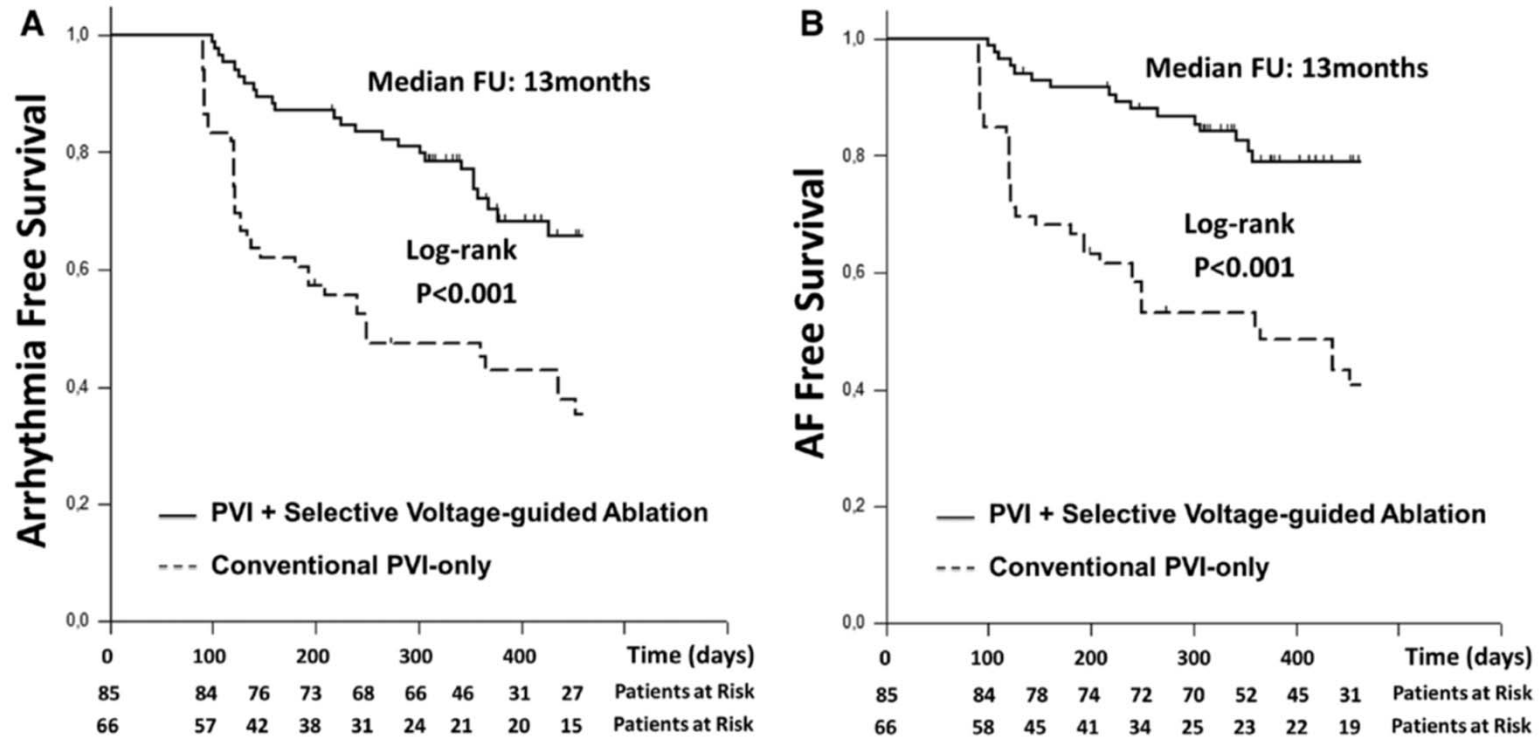
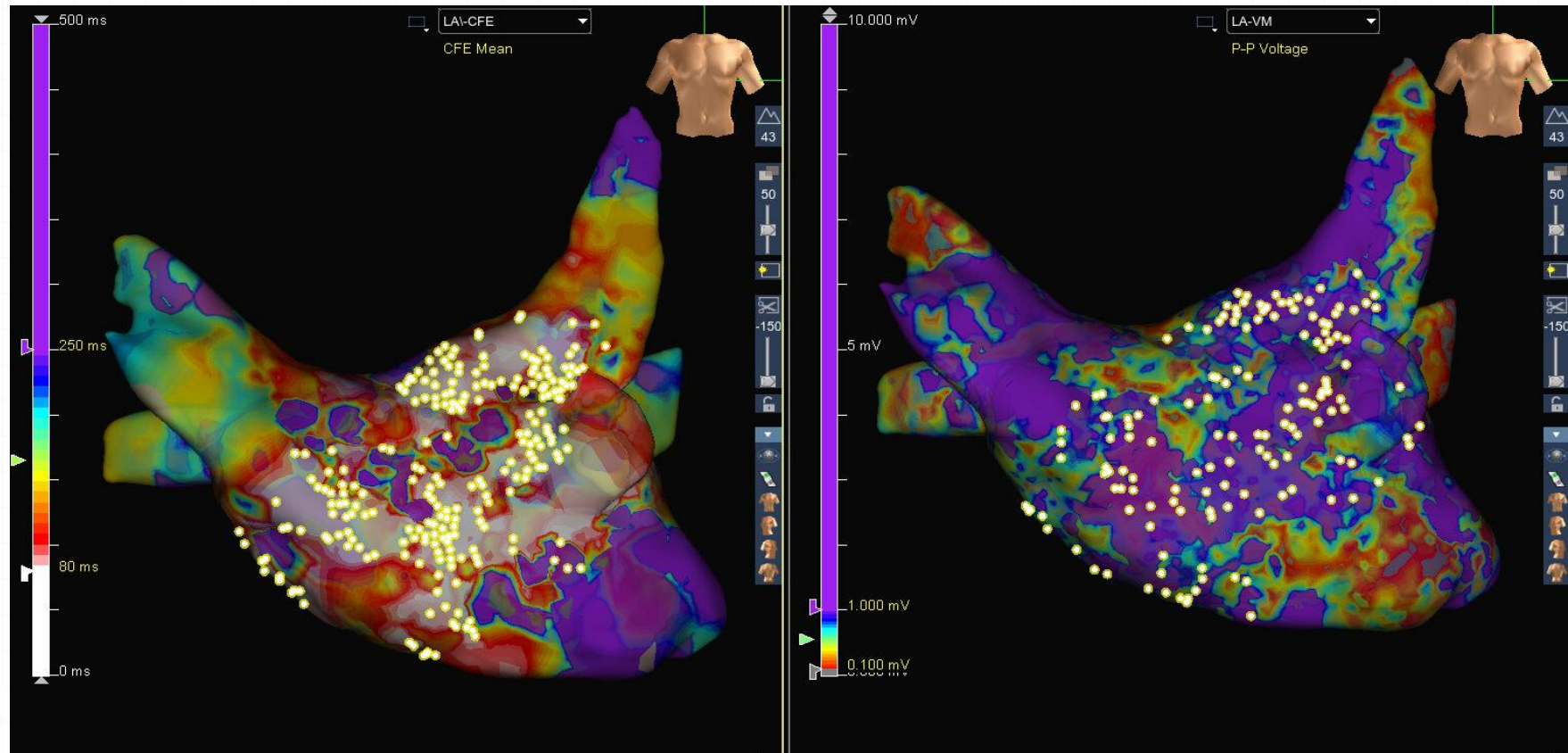
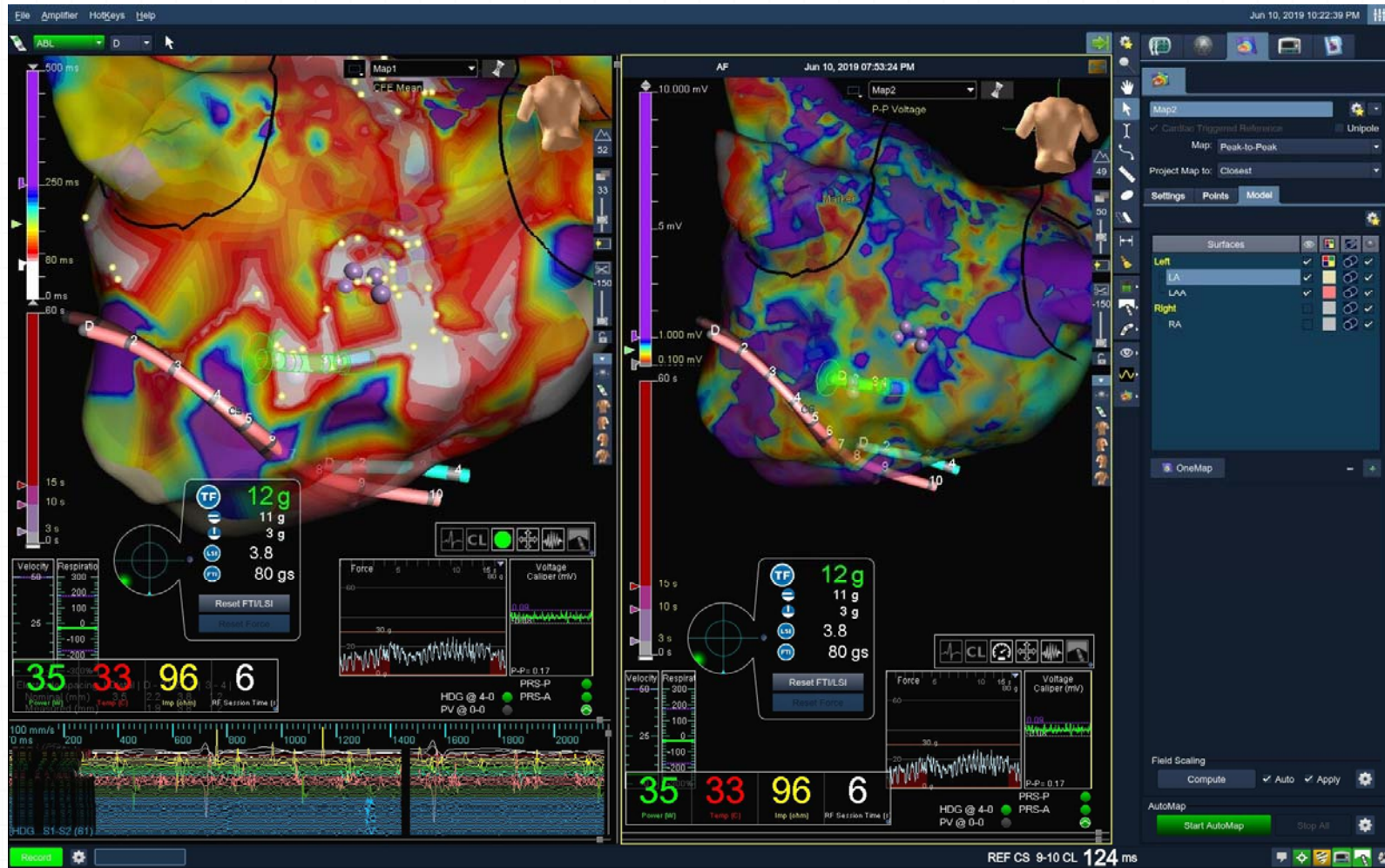


Figure 5. Kaplan–Meier curves illustrating freedom from any atrial arrhythmia (**A**) and freedom from atrial fibrillation (AF; **B**) at median follow-up (FU) of 13 months (Q1–Q3: 11–15) in patients undergoing PVI+Selective substrate-based ablation vs conventional pulmonary vein isolation (PVI)-only approach. **A**, Arrhythmia free survival selective voltage-guided ablation vs PVI. **B**, AF free survival selective voltage-guided ablation vs PVI.

CFAE and Voltage Map



Low Voltage and Fractionation Guided Ablation



Trial Outcomes of Substrate-based Ablation

Table 1 Summary of trial outcomes of substrate-based ablation

	Rhythm during mapping	Mapping catheter (electrode size)	Mapping density (mean ± SD points per map)	Control group N (PAF, PsAF)	Study group N (PAF, PsAF)	Control intervention	LVA intervention	F/U (months)	Arrhythmia-free survival (control vs. study)	Additional electrogram features?
Schreiber 2017 [5]	Sinus rhythm	Ablation (3.5 mm)	> 100	No LVA n = 49 (39, 10)	< 0.5 mV n = 92 (34, 58)	PVI alone	PVI + BIFA + L	12	84% vs. 69% P = 0.16	None
Yagishita 2017 [9]	AF	Ablation (3.5 mm)	166 ± 62	No LVA n = 42 (15, 27)	< 0.5 mV n = 159 (22, 137)	PVI alone	PVI + HI	12	71% vs. 72% P = 0.746	None
Yamaguchi 2016 [6]	Sinus rhythm	Ablation and mapping (4 mm and 1 mm)	576 ± 150	No LVA n = 62 (15, 47)	< 0.5 mV n = 39 (18, 21)	PVI alone	PVI + HI	32	79% vs. 72% P = 0.400	None
Jadidi 2016 [3]	AF	Mapping (1 mm)	1024 ± 124	Unselected n = 66 (0, 66)	Unselected n = 85 (0, 85)	PVI alone	PVI + H + RA (further ablation only to terminate AF)	13	47% vs. 69% P < 0.001	< 0.5 mV, fractionation, rotational activity, rapid local activation
Yang 2016 [7]	Sinus rhythm	Mapping (1 mm)	628 ± 212	Unselected n = 78 (0, 78)	Unselected n = 86 (0, 86)	Stepwise	PVI + HI	30	51% vs. 70% P = 0.011	< 1.3 mV, > 50 ms, ≥ 3 deflections
Cutler 2016† [4]	Sinus rhythm	Ablation (not stated)	Not stated	Unselected n = 76 (0, 76)	Unselected n = 65 (0, 65)	PVI + PWI (discretionary)	PVI + PWI	12	57% vs. 80% P = 0.005	None
Kottkamp 2016 [2]	Sinus rhythm	Ablation (4 mm)	100–120	No LVA n = 13 (0, 13)	< 0.5 mV n = 18 (0, 18)	PVI alone	PVI + BIFA	12	69% vs. 72% P = 0.742	None
Rolf 2014 [1]	Sinus rhythm	Mapping and ablation (2.1 and 4 mm)	115 ± 35	No LVA n = 131 (56, 75) With LVA n = 26 (9, 17)	< 0.5 mV n = 47 (6, 41)	PVI alone	PVI + HL	12	62% vs. 27% vs. 70%	None

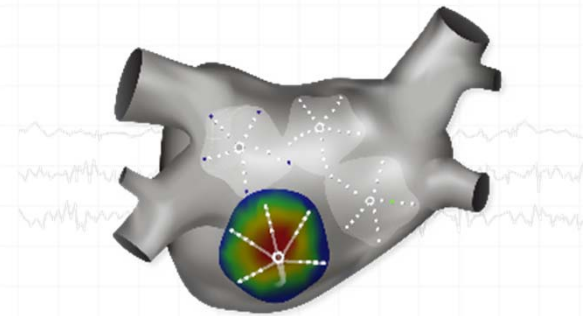
References are highlighted within the table

PVI, pulmonary vein isolation; H, homogenisation; I, isthmus; L, linear; T, transition zone; LVA, low voltage areas; PWI, posterior wall isolation; BIFA, box isolation of fibrotic area; RA, right atrium



CARTOFINDER Module

- Expands the CARTO[®] 3 System mapping capabilities to irregular arrhythmia, identifying repetitive focal and rotational activations.
- Data collected with PENTARAY[®] Catheter, ensuring contact, during arrhythmia
- Annotation of unipolar signals
- Identification of Regions of interest (ROI) for objective interpretation
 - Repetitive Rotational patterns
 - Repetitive Focal patterns



Examples of Repetitive Atrial Activation Patterns

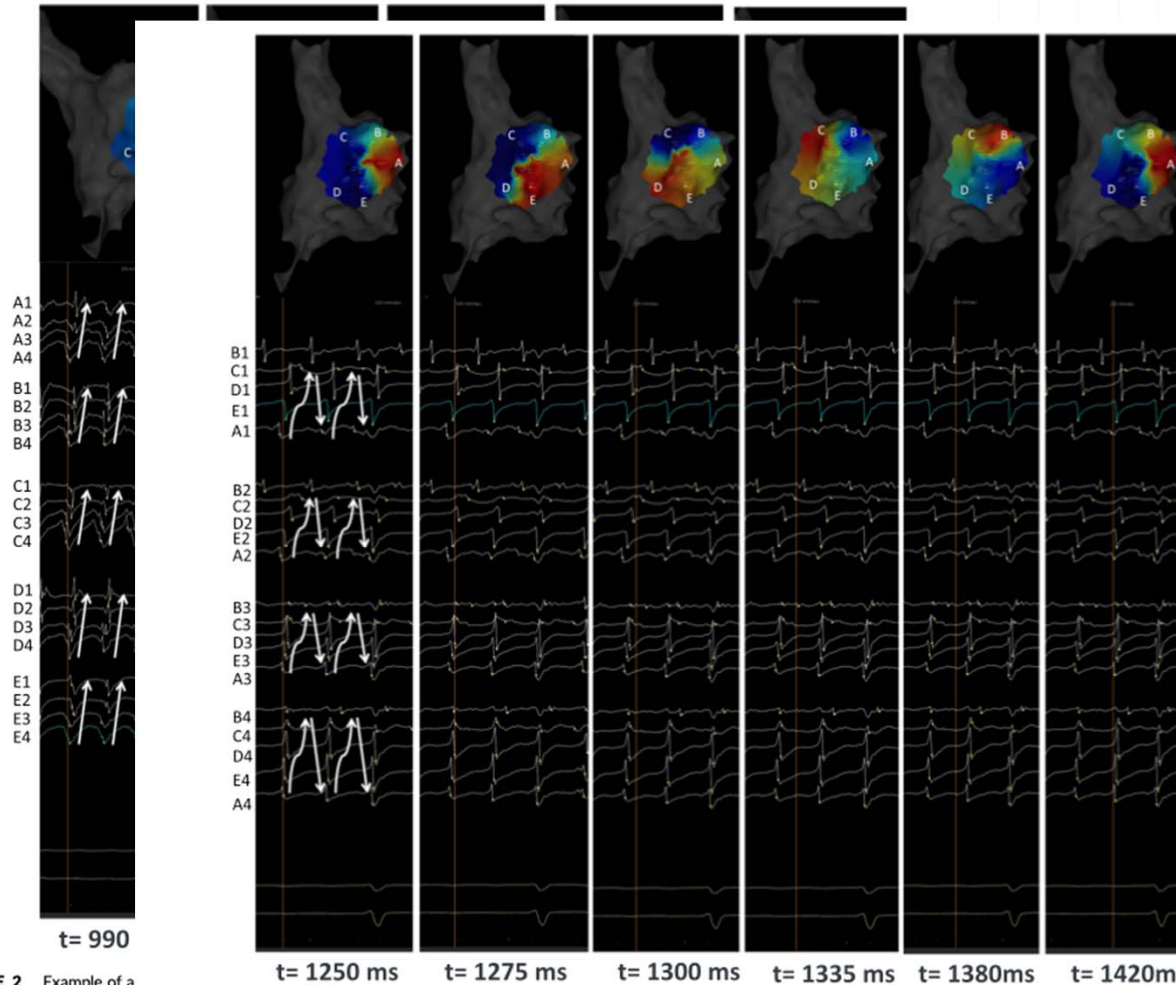


FIGURE 2 Example of a time window of 990 to 1030 recorded at each electrode (spline) show a centrifugal pr

FIGURE 3 Example of a RAAP_{rotational}: PentaRay positioned at the lateral wall of the right atrium. Subsequent panels show the propagation during a time window of 1250 to 1420 ms of a 30 seconds registration during ongoing atrial fibrillation. The color-coding, as well as the unipolar fibrillatory EGMs recorded at each electrode (here organized per radius with electrode 4 as the most proximal and electrode 1 as the most distal per spline A to E), show a repetitive rotational propagation consistent with a RAAP_{rotational}. EGM, electrogram; RAAP, repetitive atrial activation pattern

Distribution of Repetitive Atrial Activation Patterns

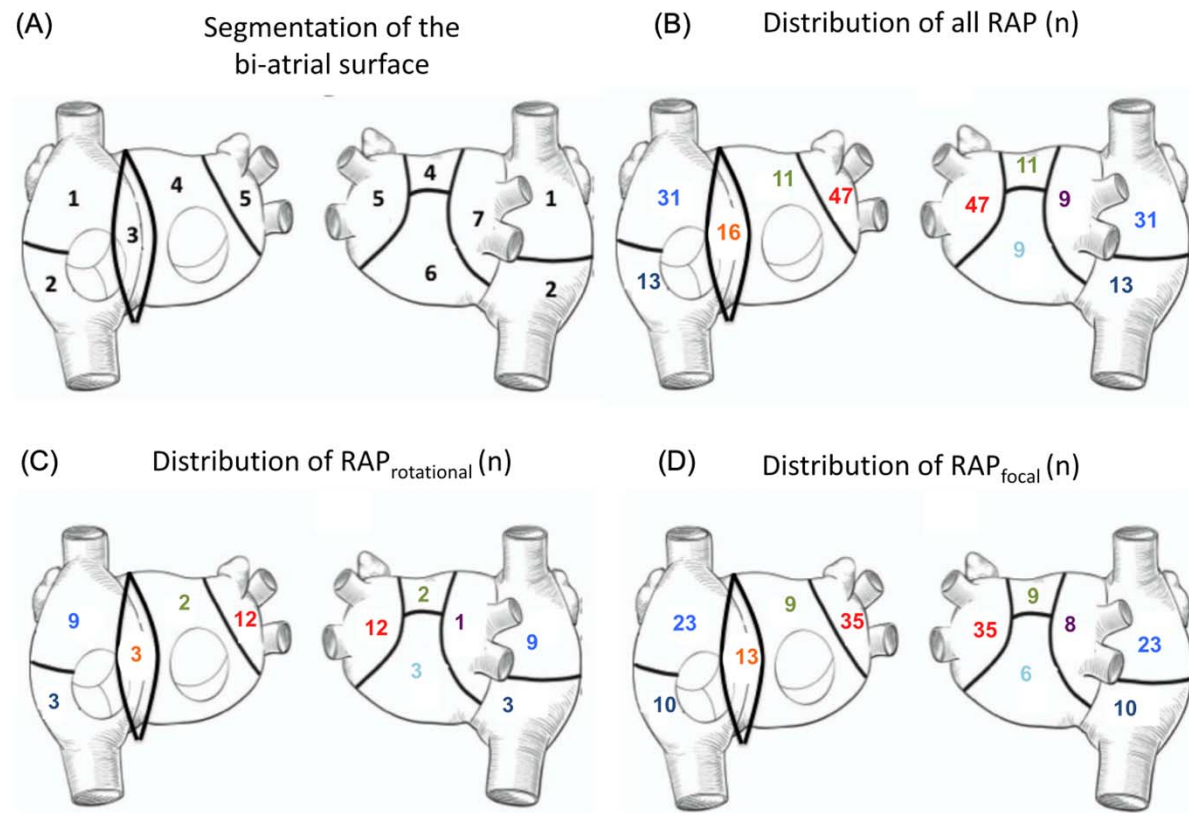


FIGURE 4 Panel A: To classify the spatial distribution of RAAPs, the biatrial surface was divided in 7 regions. Four regions were defined in the left atrium, 2 in the right atrium, and 1 in the anterior interatrial septum. Because of their proximity, left PVs were grouped with the left appendage into 1 region en bloc. Similarly, the right atrial appendage was grouped with the upper right atrium. Panel B: total number of identified RAAPs per region for all 14 patients. Panel C: number of RAAP_{rotational} per region for all 14 patients. Panel D: number of RAAP_{focal} per region for all 14 patients. RAAP, repetitive atrial activation pattern

Focal Rotationan Activations in LA & RA

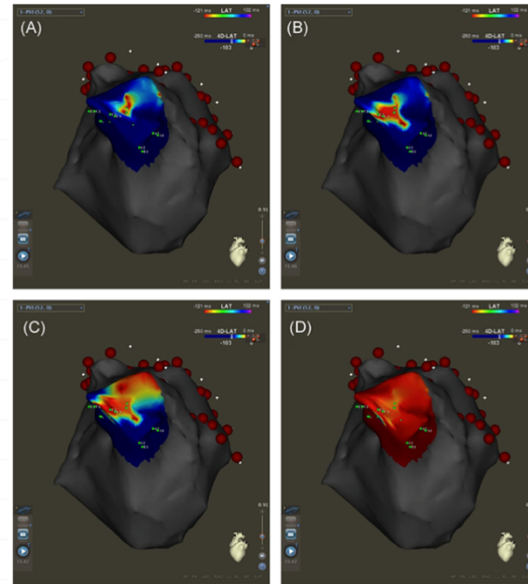


FIGURE 1 Snapshots of 4D-LAT map displaying focal activation patterns in the left atrial appendage. Red represents activation timing of electrograms. Activity occurs at the middle of a PentaRay catheter (A). Then, activity spreads to the periphery of the mapping area over time (B→C→D). LAT, local activation time

TABLE 2 Focal and rotational activations in each atrial region

	LA (n = 80)					RA (n = 64)			P value*
	Anteroseptum (n = 67)	Appendage (n = 70)	Inferior (n = 80)	Lateral (n = 70)	Posterior (n = 63)	Anteroseptum (n = 46)	Appendage (n = 63)	Lateral (n = 62)	
Presence of focal activation	46%	91%	70%	80%	16%	72%	87%	81%	<.001
No. of focal activation events (interquartile range)/30 s	8 (4-15)	28.5 (15-54)	7 (4-11)	13 (6-19)	6 (3-11)	8 (6-18)	15 (11-28)	11.5 (7-19)	<.001
The number of electrodes displaying focal activation per map	2.1 ± 1.8	5.4 ± 3.1	1.8 ± 1.3	4.1 ± 2.9	1.4 ± 0.5	3.1 ± 2.5	5.2 ± 3.3	3.3 ± 2.2	<.001
Presence of rotational activation	6%	14%	25%	11%	2%	0%	6%	13%	<.001
No. of rotational activation events (interquartile range)/30 s	13.15 (10.5-17.4)	18.2 (12.7-20.6)	16.4 (11.3-23)	18 (14.1-21.9)	13.8		18.2 (15.1-20.6)	14.8 (12.6-17.2)	.6

*Whether there were differences over the eight atrial regions.

Distribution of Focal and Rotational Activation

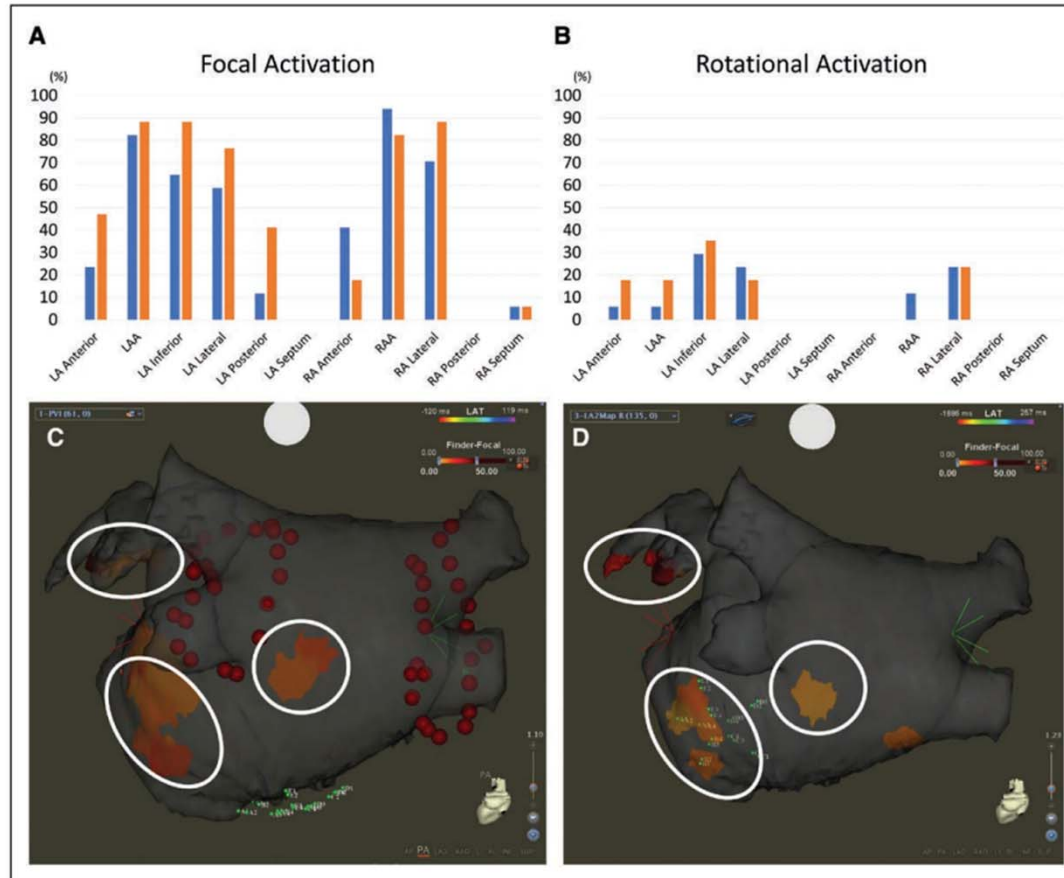


Figure. Distribution of focal and rotational activation during the de novo and repeat ablation procedure.

Percentages of patients in whom focal (A) and rotational activation (B) was observed at at least one site in each atrial region during the de novo (blue) and repeat (orange) ablation procedure. Focal activation identified by CARTOFINDER during the de novo (C) and repeat ablation procedures (D) in the same patient. The orange or red areas represent focal activation identified by CARTOFINDER. Darker colors represent more frequent focal events. Focal activation was identified in the postero-lateral wall of the left atrium, posterior wall near the left inferior pulmonary vein, and left atrial appendage during both ablation procedures (white circle). LA indicates left atrial; LAA, left atrial appendage; RA, right atrial; and RAA, right atrial appendage.

Ablation guided by CARTOFINDER

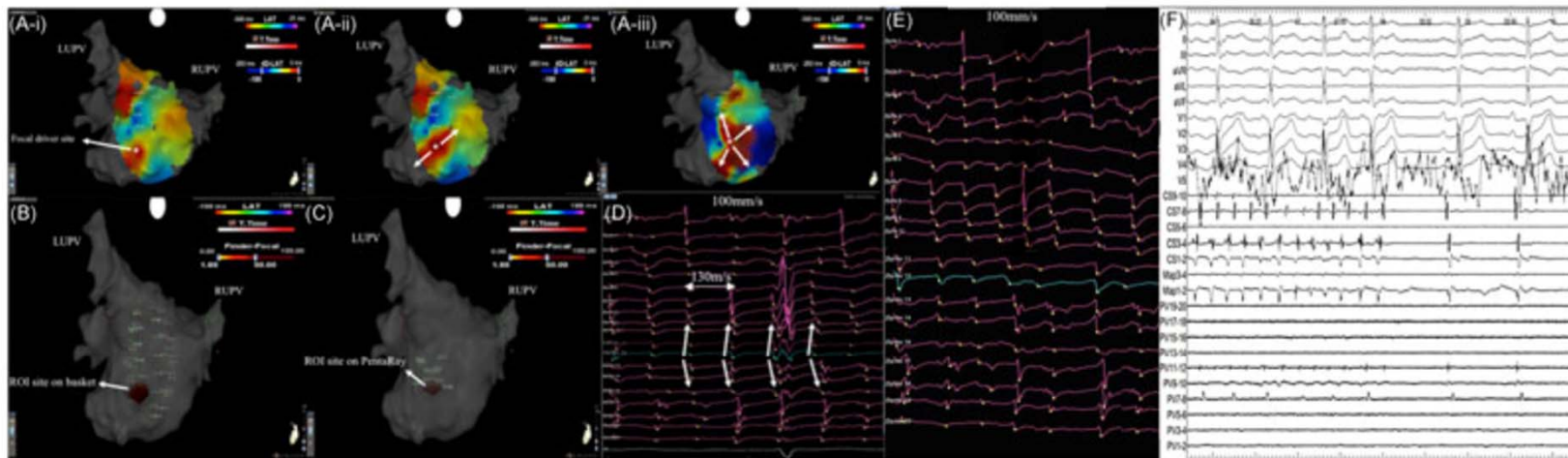
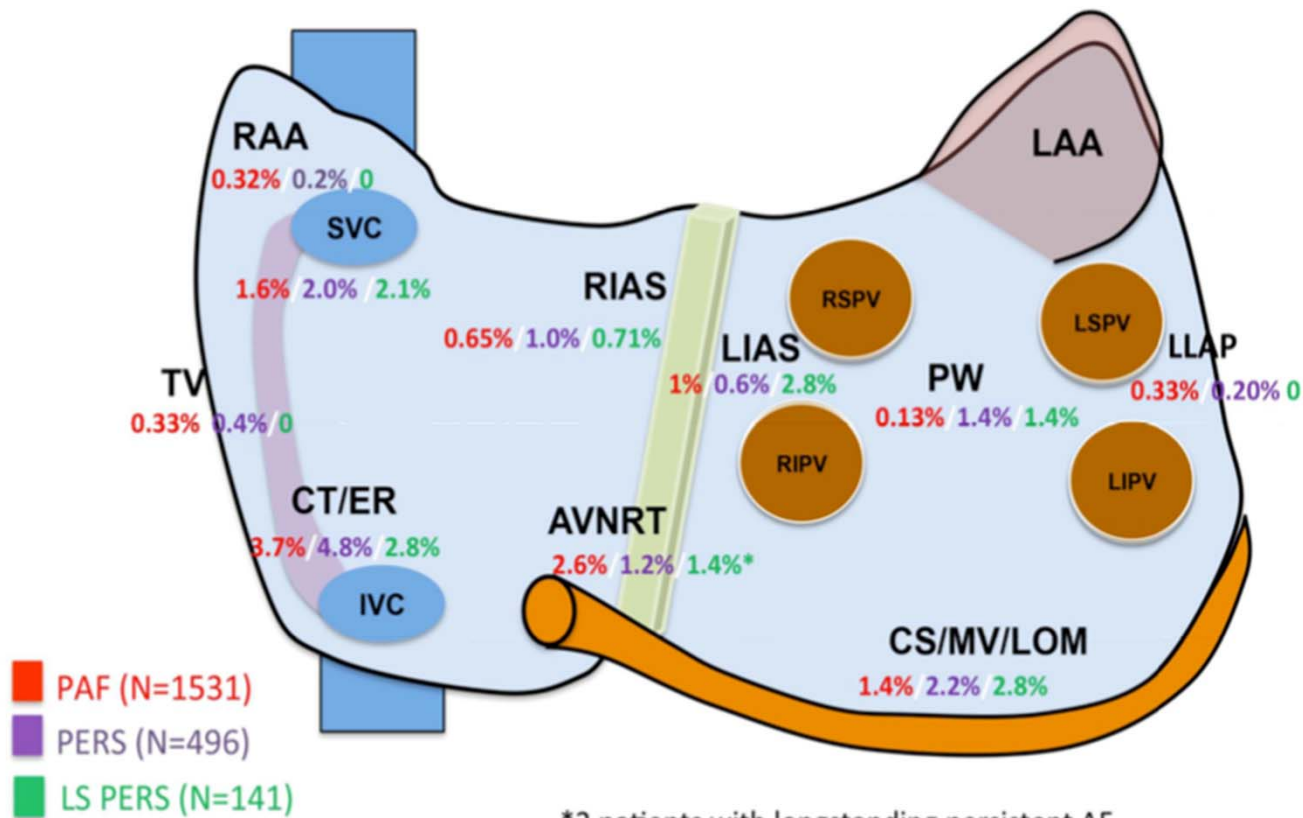


FIGURE 5 A focal driver mapped to inferior-posterior wall on (Ai-iii) still CARTOFINDER wavefront maps, (B) ROI map created with simultaneous mapping with basket catheter, (C) ROI map created with sequential mapping with PentaRay catheter, (D) corresponding unipolar electrograms recorded on PentaRay with the electrogram in green highlighting the electrode recording the initial signal at the focal driver site with radial spread to the surrounding electrodes. (E) Unipolar electrograms recorded on PentaRay between episodes of repetitive focal activations. (F) Electrograms demonstrating AF termination to sinus rhythm during ablation at the driver site. AF, atrial fibrillation; LUPV, left upper pulmonary vein; ROI, region of interest; RUPV, right upper pulmonary vein

Distribution of Non-PV Triggers

RAA=right atrial appendage
 TV=tricuspid valve
 CT=crista terminalis
 ER=eustacian ridge
 SVC=superior vena cava
 AVNRT=AV node reentrant tachycardia

LAA=left atrial appendage
 MV=mitral valve
 CS=coronary sinus
 LOM=ligament of Marshall
 LLAP=left lateral accessory pathway
 PW=posterior wall



*2 patients with longstanding persistent AF



Protocol for initiating Non-PV Triggers

- Withhold antiarrhythmic agents for five half-lives and beta-blockers for at least 24 hours
- Baseline infusion of a vasoconstrictor (e.g., phenylephrine).
- Graded infusion of isoproterenol using up to 20-30ug/min for at least 10 minute.
- If no effect with isoproterenol infusion, burst pacing into AF and then cardioversion during low-dose isoproterenol infusion (2-6ug/min).
- Use of adenosine bolus or burst atrial pacing during low-dose isoproterenol infusion.



Adenosine-Provoked AF from Non-PV Foci

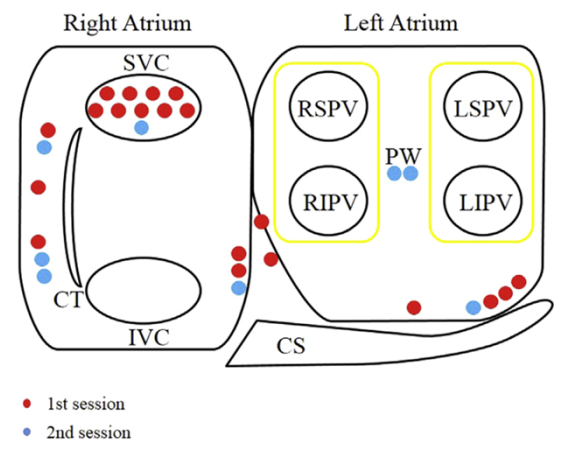
TABLE 1 Clinical Characteristics of Patients With and Without ATP-Provoked AF

	ATP-AF (+) (n = 26 [5.6%])	ATP-AF (-) (n = 438 [94.4%])	Univariable p Value	Multivariable p Value	HR	95% CI
Age, yrs	58.7 ± 12.8	62.6 ± 10.8	0.083	0.136		
Female	11 (42.3)	121 (27.6)	0.107	0.034	2.52	1.069-5.929
SHD	1 (3.9)	50 (11.4)	0.231			
Hypertension	15 (57.7)	251 (57.3)	0.969			
Body mass index, kg/m ²	24.0 ± 3.8	24.3 ± 3.7	0.692			
CHADS ₂ score	0.73 ± 0.96	0.79 ± 0.93	0.745			
CHA ₂ DS ₂ -VASc score	1.54 ± 1.58	1.58 ± 1.38	0.889			
LA diameter, mm	39.9 ± 5.5	40.3 ± 5.8	0.724			
LV ejection fraction, %	65.5 ± 9.0	66.5 ± 7.0	0.476			
proBNP, pg/ml	270 ± 356	332 ± 1,033	0.801			
hs-CRP, mg/dl	0.17 ± 0.28	0.24 ± 0.81	0.662			
Estimated GFR, ml/min	77.3 ± 17.8	71.1 ± 19.4	0.114	0.393		

Values are mean ± SD or n (%).

AF = atrial fibrillation; ATP = adenosine triphosphate; CHADS₂ score = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus (1 point) and stroke/transient ischemic attack (2 points); CHA₂DS₂-VASc score = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; LA = left atrium; LV = left ventricular; proBNP = pro-B-type natriuretic peptide; SHD = structural heart disease.

FIGURE 2 Distribution of the Origins of ATP-Provoked AF



Systemic Approach to Non-PV Trigger Mapping

1. Analysis of the initiating P-wave morphology on the 12-lead ECG when the P wave does not overlap with the T wave or QRS
2. Analysis of the earliest endocardial site of activation at the multipolar CS and CT/SVC catheters referenced to P-wave onset.
3. Analysis of the activation patterns at the multipolar CS and CT/SVC catheters.
4. Detailed mapping of the region of origin outside the PVs by manipulating the circular mapping catheters and the ablation catheters guided by the P-wave morphology and the activation pattern from the multipolar CS and CT/SVC catheters.



Non-PV Trigger Localization According to CS

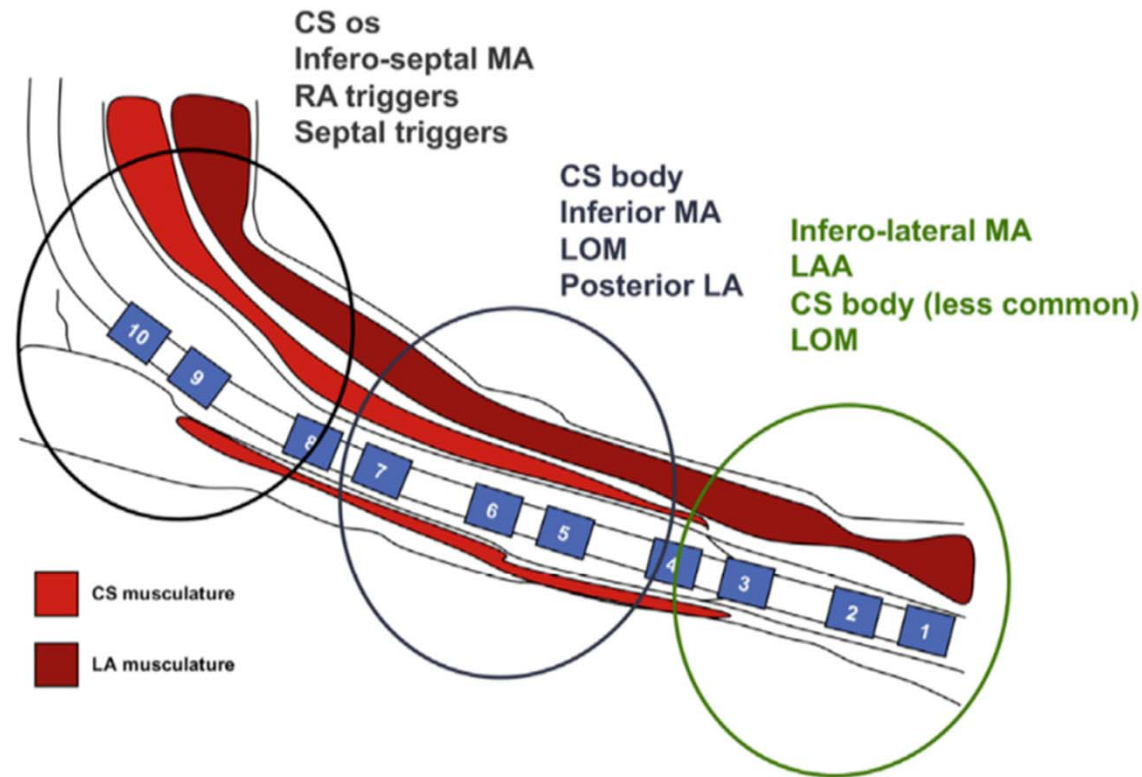


Figure 5 Diagram representing the possible sites of origin of non-pulmonary vein atrial fibrillation triggers according to earliest activation recorded at the coronary sinus (CS) catheter. CS = coronary sinus; LA = left atrial; LAA = left atrial appendage; LOM = ligament of Marshall; MA = mitral annulus; os = ostium.

Targets for Ablation of Non-PV Triggers

Table 4: Targets for Ablation of AF Originating from Non-pulmonary Vein Areas

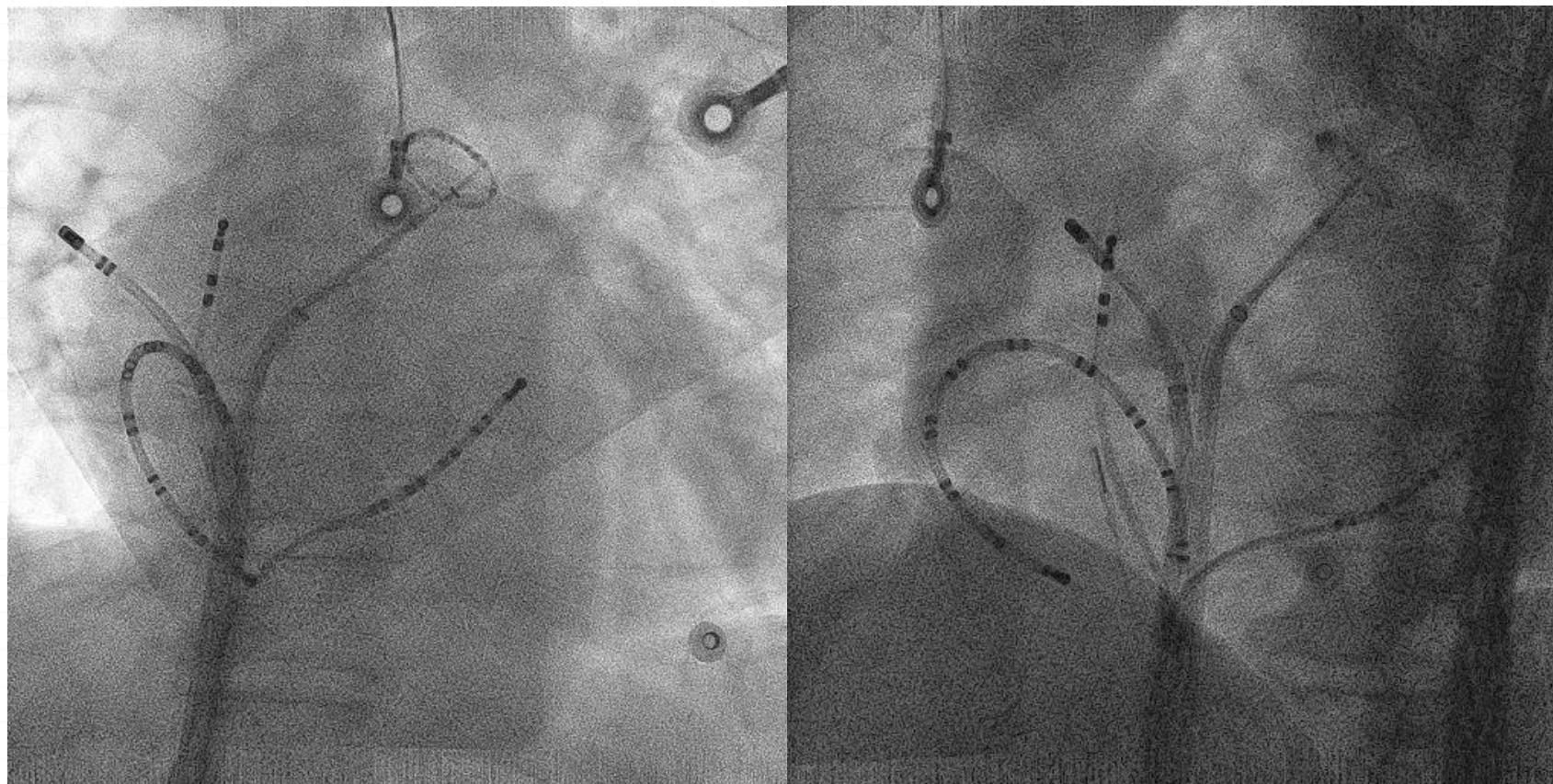
AF Initiators	Target Sites	Mapping Tools
Right Side		
Inferior vena cava, superior vena cava	Breakthrough sites around right atrium–vena cava junction for an isolation	Circular catheter, Array, Grid, PentaRay or Rhythmia
Crista terminalis	Earliest crista terminalis activation site for a focal ablation	Unipolar recording with a multipolar catheter, Array, Grid, PentaRay or Rhythmia
Coronary sinus	Connection sites between the coronary sinus and atrial musculature for an isolation	Array, PentaRay or Rhythmia
Left Side		
Left atrial free wall, septum, appendage, mitral annulus	Earliest activation site for a focal ablation	Unipolar recording with a multipolar catheter, Array, Grid, PentaRay or Rhythmia
Ligament of Marshall (LOM)	Earliest LOM potential for a focal ablation	Multipolar recording of triple potentials during ectopy and direct mapping of LOM potentials by microelectrode catheter, Array, Grid, PentaRay or Rhythmia
	Connection sites between the left atrium and LOM for an isolation	Multipolar recording of triple potentials during ectopy and direct mapping of LOM potentials by a microelectrode catheter, Array, Grid, PentaRay or Rhythmia

Array = EnSite™ Array™ Noncontact Mapping System (Abbott); Grid = Advisor™ HD Grid Mapping Catheter (Abbott); LOM = ligament of Marshall; PentaRay = PentaRay® Catheter (Biosense Webster); Rhythmia = Rhythmia Mapping System and InntellaMap Orion™ Mapping Catheter (Boston Scientific). Source: Higa et al., 2006.³³ Reproduced with permission from Elsevier.

Our protocols

- Withhold antiarrhythmic agents for five half-lives and beta-blockers for at least 24 hours
- Isoproterenol infusion starting at 5 μg and incrementing every 3-5 minutes to 10, 15, and 20 μg based on the heart rate response
- If no effect with isoproterenol infusion, use of adenosine 24mg bolus IV
- If no effect with isoproterenol or adenosine, burst pacing into AF.

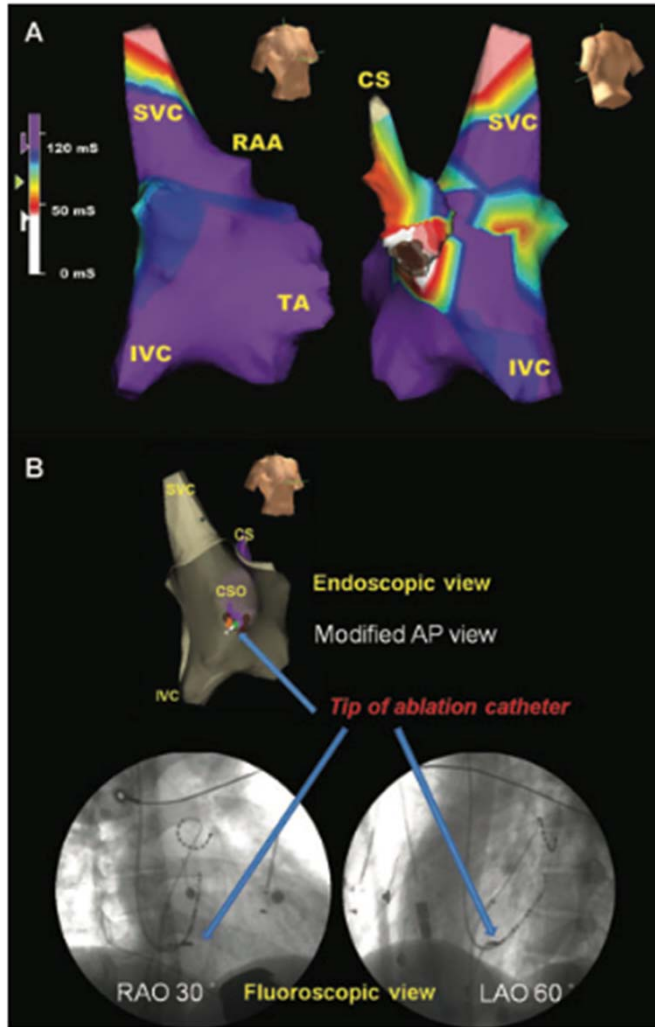
My Catheter Position for Trigger Mapping



Pitfalls of Non-PV trigger mapping

- Given the transient nature of non-PV triggers and/or rapid degeneration into AF, detailed activation mapping to localize the precise site of origin of a trigger may not be possible.
- As part of the trigger induction protocol, multiple cardioversions are typically necessary whenever AF is induced, with the endpoint of mapping the initial trigger beat leading to postcardioversion AF.

CFAEs from Non-PV Ectopy



Tracing A.



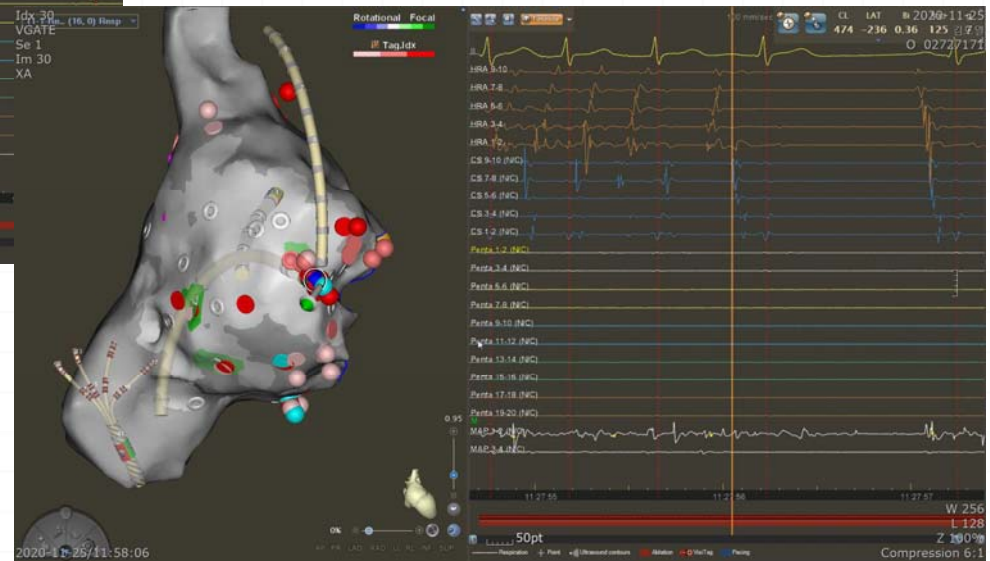
Tracing B.



Tracing C.



Non-PV Trigger Ablation guided by CARTOFINDER



Summary

- Patient-specific ablation targeting low voltage area acquired by high-density voltage map could be a promising additional strategy beyond PVI.
- Ablation of sites with distinctive electrogram within low voltage area in addition to PV isolation could be a more effective ablation strategy for persistent AF.
- Ablation targeting focal sources detected by CARTOFINDER could be another promising ablation strategy.
- Ablation of non-PV triggers might be more important for patients with persistent forms of AF and for those patients who undergo repeat ablation procedures in whom all PVs are found to be isolated.



Thanks for your attention !!